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Aerobic, Cu-catalyzed desulfitative C–C bond-forming reaction of ketene dithioacetals/vinylogous thioesters and arylboronic acids†

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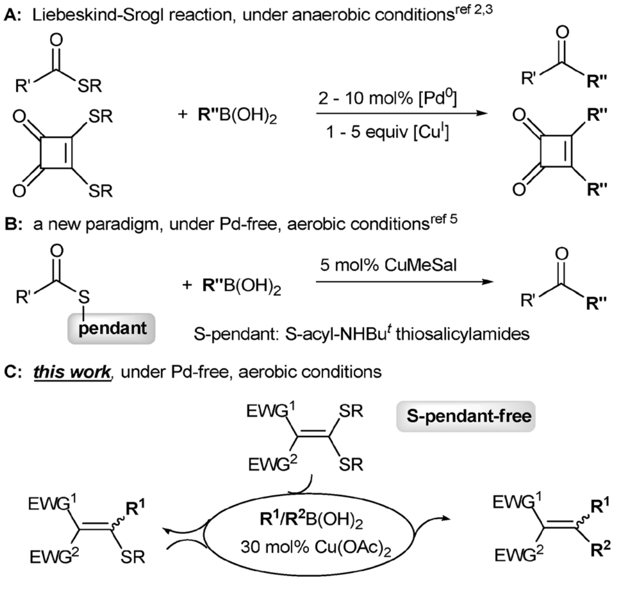
A new Cu-catalyzed thioorganic–boronic acid desulfitative C–C bond-forming reaction involving ketene dithioacetals/ vinylogous thioesters is reported to proceed without the assistance of ligating S-pendant. Vinylogous thiolesters and tetrasubstituted olefins were prepared by this reaction in which Cu catalyst plays a dual role under aerobic conditions.

Transition metal-catalyzed C–C bond-forming reactions involving boronic acids offer particular advantages in terms of tolerance towards a variety of functional groups.[1] Therefore, Pd-catalyzed thioester–boronic acid desulfitative coupling for the synthesis of ketones developed by Liebeskind and Srogl in 2000[2a] has earned a place in the list of this rapidly growing field.[2,3] All published thioorganic–boronic acid couplings have required catalytic quantities of Pd^0 and at least stoichiometric amounts of Cu^I under neutral, anaerobic conditions (Scheme 1A), except for a recent example of aerobic Pd^{II} and Cu^{II} co-catalyzed coupling of mercaptoacetylenes and arylboronic acids.[4] In 2007, Liebeskind and coworkers reported an aerobic Cu-catalyzed, Pd-free coupling of thioesters with boronic acids.[5a] This low-cost catalytic cross-coupling is mechanistically unique and is of key interest to the synthetic community,[5b] however, the method is severely limited to thioesters[5] and requires an initial buildup of a precursor with appropriately positioned S-pendant, for example, S-aryl-NH*t*Bu thiosalicylamides, acting as a templating ligand for Cu catalyst (Scheme 1B).[5] Clearly, it is in great demand to expand the scope of this cheap pathway, especially to expand its thioorganics to those compounds without having to incorporate the S-pendant.[3,5]

As part of our continuing research on the chemistry of functionalized ketene dithioacetals,[6,7] we report herein an aerobic Cu-catalyzed thioorganic–boronic acid coupling involving ketene dithioacetals/vinylogous thioesters. Different from the previous reports (Scheme 1A and 1B),[2–5] this Pd-free coupling procedure represents a dual catalysis of Cu for the activation of thioorganics under aerobic conditions without the assistance of S-pendant and provides a novel C–C bond-forming method for the synthesis of vinylogous thioesters[8] and tetrasubstituted olefins[9] from readily available sulfur substrates (Scheme 1C).

The starting materials, ketene dithioacetals **1**, were conveniently prepared by the published protocols in high yields.[10] Initially, the reaction of diethyl 2-(bis(benzylthio)-methylene) malonate **1a** (1.0 mmol) and *p*-chlorophenylboronic acid **2a** (3.0 mmol) in DMF was investigated as a model system to screen Cu catalysts and reaction conditions (Table 1). Only small amount of homocoupling product of **2a**, 4,4′-dichlorobiphenyl, was obtained when the reaction was carried out at 60 °C for 30 h under open air with 0.1 or 0.2 equiv. of $Cu(OAc)_2$ as catalyst (entries 1 and 2). To our delight, the desired product, vinylogous thioester **3a**, could be isolated in 43% yield at 100 °C for 60 h catalyzed by 0.2 equiv. of $Cu(OAc)_2$ (entry 3). Increasing the catalyst amount or elevating temperature proved to facilitate the coupling (entries 4–6). With 0.3 equiv. of $Cu(OAc)_2$ at 130 °C for 60 h, **3a** was obtained in 70% yield (entry 7). However, higher temperature led to decreasing yield (entry 8) as a large amount of biphenyl was formed. Additionally, higher yield of **3a** could be achieved with 6.0 equiv. of **2a** (entry 9). It should also be noted that aerobic conditions proved to be required for the catalytic cycle since **3a** was obtained only in 10% yield under



Scheme 1 Thioorganic–boronic acid C–C couplings.

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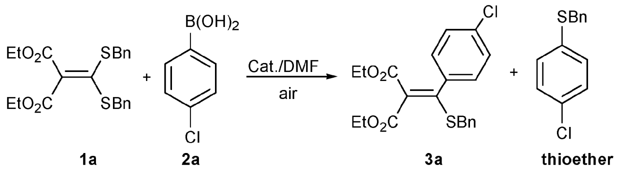
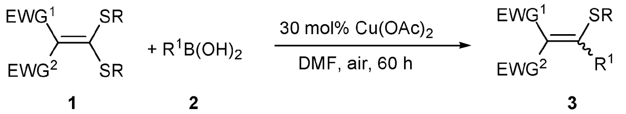
Table 1 Screening of reaction conditions[a]

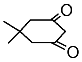


Entry	Cat. (equiv.)	T/°C	Time/h	Yield (%)[b]
1	$Cu(OAc)_2$ (0.1)	60	30	nd[c]
2	$Cu(OAc)_2$ (0.2)	60	30	nd[c]
3	$Cu(OAc)_2$ (0.2)	100	60	43[d]
4	$Cu(OAc)_2$ (0.3)	100	60	51[e]
5	$Cu(OAc)_2$ (0.3)	130	30	61
6	$Cu(OAc)_2$ (0.3)	130	40	62
7	$Cu(OAc)_2$ (0.3)	130	60	70[f]
8	$Cu(OAc)_2$ (0.3)	Reflux	60	29
9	$Cu(OAc)_2$ (0.3)	130	60	83[g]
10	$Cu(OAc)_2$ (0.3)	130	60	10[h]
11	$Cu(O_2CCF_3)_2$ (0.3)	130	60	58
12	$CuSO_4$ (0.3)	130	60	56
13	CuTc (0.3)	130	60	49
14	CuMeSal (0.3)	130	60	44
15	CuBr (0.3)	130	60	9.0
16	$CuBr_2$ (0.3)	130	30	nd[c]

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), DMF (4.0 mL), air. [b] Isolated yield. [c] Not detected. [d] **1a** was recovered in 34% yield. [e] **1a** was recovered in 25% yield. [f] Thioether was isolated in 71% yield. [g] Yield with 6.0 equiv. of **2a**. [h] Yield under N_2.

Table 2 $Cu(OAc)_2$-catalyzed desulfitative coupling reaction of **1** and **2**[a]



Entry	1	EWG^1, EWG^2	R	2, R^1	Yield (%)[b]
1				**2a**: 4-ClC_6H_4	**3a**: 70 (83)
2				**2b**: Ph	**3b**: 61 (71)
3				**2c**: 3-$NO_2C_6H_4$	**3c**: 58 (79)
4				**2d**: 4-MeC_6H_4	**3d**: 64 (78)
5	**1a**	CO_2Et, CO_2Et	Bn	**2e**: 3-MeC_6H_4	**3e**: 60 (82)
6				**2f**: 2-MeC_6H_4	**3f**: 57 (77)
7				**2g**: 4-PhC_6H_4	**3g**: 61 (78)
8				**2h**: 2-naphthyl	**3h**: 59 (74)
9				**2i**: (*E*)-styryl	nd[c]
10	**1b**	CO_2Et, CO_2Et	Me	**2b**: Ph	**3i**: 71 (86)
11	**1c**	CO_2Et, CO_2Et	Et		**3j**: 72 (82)
12	**1d**	CO_2Me, CO_2Me	Bn		**3k**: 63 (77)
13[d]	**1e**	MeCO, MeCO	Bn		**3l**: 41 (51)
14[e,f]	**1f**	CO_2Et, MeCO	Me		**3m**: 60 (76)
15[e,f]	**1g**	MeCO, PhCO	Bn		**3n**: 55 (67)
16[d,f]	**1h**	CO_2Et, NO_2	Me		**3o**: 62 (78)
17	**1i**		Bn		nd[c]
18	**1j**	MeCO, —	Me		nd[c]
19	**1k**	CO_2Et, —	Me		nd[c]

[a] Reaction conditions: **1** (1.0 mmol), **2** (3.0 mmol), $Cu(OAc)_2$ (0.3 mmol), DMF (4.0 mL), 130 °C, air, 60 h. [b] Isolated yield. Yield in parentheses was obtained by using up to 6.0 equiv. of **2**. [c] Not detected. [d] Reaction was performed at 110 °C for 30 h. [e] Reaction was performed at 110 °C for 50 h. [f] Yield based on a mixture of two isomers.

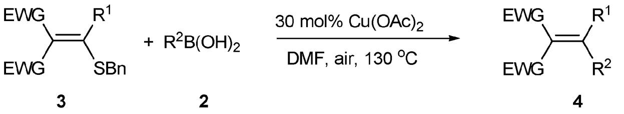
N_2 (entry 10). Similar to the previous results,[5a,c] thioether was obtained as a by-product in the reaction (entry 7). Next, different Cu catalysts were examined. As presented in Table 1, $Cu(O_2CCF_3)_2$, $CuSO_4$, copper(I)-thiophene-2-carboxylate (CuTC), and Cu^I-3-methylsalicylate (CuMeSal) were effective catalysts and gave **3a** in 44–58% yields (entries 11–14). However, CuBr was less effective and $CuBr_2$ was ineffective for the reaction (entries 15 and 16).[5a]

Dieter *et al.* reported the synthesis of vinylogous thioesters by the reaction of organocuprates with α-oxo ketene dithioacetals under N_2.[11] However, our approach creates a newly catalytic pathway for preparing vinylogous thioesters[8] by the conjugate addition using boronic acids as mild nucleophiles[1] and represents the first example of Cu-catalyzed desulfitative C–C coupling under Pd-free conditions without the assistance of ligating S-pendant group. Thus, the scope of the reaction was explored under the conditions as described in Table 1, entry 7, considering both the yield and the amount of boronic acids.

The results shown in Table 2 suggested that the reaction of ketene dithioacetal **1a** with boronic acids **2** bearing phenyl (entry 2), electron-deficient (entries 1 and 3) and electron-rich aryl group (entries 4–8) could afford the desired vinylogous thioesters **3a–h** in good yields. However, alkenyl boronic acid, such as (*E*)-styrylboronic acid **2i**, was proven ineffective (entry 9). It was found that higher yields of **3** could be obtained in the case of substrates **1** with dimethylthio/diethylthio functional groups (entry 2 *vs.* entries 10 and 11). Similarly, vinylogous thioesters **3k** and **3l** were obtained in 63% and 41% yield, respectively, from **2b** with **1d** and **2b** with **1e** (entries 12 and 13). In addition, reactions of **2b** with ketene dithioacetals **1f–h** bearing two different EWGs afforded **3m–o** in good yields (entries 14–16). Whereas, the vinylogous thioesters were not obtained from those ketene dithioacetals having a cyclic 1,3-dicarbonyl unit (**1i**, entry 17) or bearing only one EWG (**1j** and **1k**, entries 18 and 19). It is necessary to point out that the formation of biphenyls can not be avoided in all cases because Cu salt is also an efficient catalyst for the homocoupling of boronic acids.[12]

It was found that the yields of **3** could be increased by 10–20% (Table 2, yields in parentheses) when 6.0 equiv. of boronic acids **2** was used. It is worth emphasizing that these Cu-catalyzed reactions are controllable and the double C–C coupling products, tetrasubstituted olefins **4**, are detected only in trace amounts even if a large excess of boronic acids were used. By contrast, the Pd-catalyzed, Cu-mediated couplings of bisarylthio cyclobutenediones with boronic acids were difficult to ensure the formation of mono cross-coupling products (Scheme 1A).[2b]

The significance of tetrasubstituted olefins is reflected in their presence in drugs, for example, tamoxifen (an essential drug for the treatment of breast cancer).[13] Nevertheless, the synthesis of tetrasubstituted olefins is one of the most challenging subjects because of the paucity of synthetic access.[9,13,14] Fortunately, we found that tetrasubstituted olefin **4a** could be obtained in 47% isolated yield by further treatment of **3b** (0.5 mmol) with **2b** (1.5 mmol) in DMF at 130 °C for 30 h in the presence of $Cu(OAc)_2$ (0.15 mmol) under open air. Similarly, tetrasubstituted olefins **4b–e** were successfully synthesized in 48–57% isolated yields, respectively (Scheme 2).



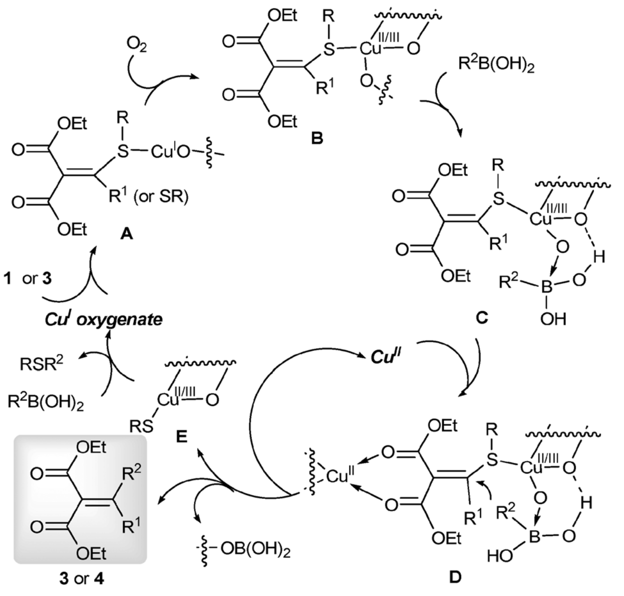
4a: EWG = CO_2Et, $R^1 = R^2$ = Ph, 47%;
4b: EWG = CO_2Me, $R^1 = R^2$ = Ph, 52%;
4c: EWG = COMe, $R^1 = R^2$ = Ph, 48%; (at 100 °C)
4d: EWG = CO_2Et, R^1 = Ph, R^2 = 4-ClC_6H_4, 53%;
4e: EWG = CO_2Me, R^1 = Ph, R^2 = 4-ClC_6H_4, 57%;

Reaction conditions: **3** (0.5 mmol), **2** (1.5 mmol), $Cu(OAc)_2$ (0.15 mmol), DMF (4.0 mL), 130 °C, air, 30 - 60 h.

Scheme 2 Synthesis of tetrasubstituted olefins.

On the basis of all of the results mentioned above and related reports,[3,5] the mechanism for the desulfitative C–C bond-forming reaction is proposed in Scheme 3. The first two steps are similar to the mechanism proposed by Liebeskind[5a] and involves, (1) the initial activation of thioorganics (ketene dithioacetal **1** or vinylogous thiolester **3**) by coordination to Cu^{I} oxygenate to form intermediate **A** which is oxidized to a higher oxidation state $Cu^{II/III}$ intermediate **B** under aerobic conditions, (2) further coordination of **B** to boronic acid to afford intermediate **C** in which the nucleophilic R^2 is directed toward the β-position of the enone. Differently, however, the coupling product **3** or **4** could not be formed at this stage because further activation is necessary.

As shown in Scheme 3, an additional activation of intermediate **C** by Cu^{II} is required to afford more reactive Cu^{II}-coordination intermediate **D**, thereby enhancing the electrophilicity of the enone and facilitating the consequent conjugated addition–elimination procedure (**D** → **3**/**4**). In fact, the two times catalytic activations of thioorganics require a little more amount of Cu catalyst. Finally, the catalytic cycle is completed by reaction of the $Cu^{II/III}$-thiolate **E**, released from the reaction, with the second (sacrificial) equivalent of the boronic acid to generate a thioether[15] and a Cu^{I} oxygenate. Therefore, it is easy to understand that substrates **1** having an acyclic 1,3-dicarbonyl and related functionality, which coordinate with Cu^{II} in a bidentate fashion, show higher reactivity towards the desulfitative coupling than those having cyclic 1,3-dicarbonyl unit or only one carbonyl group (Table 2, entries 1–16 *vs.* 17–19).[16]



Scheme 3 Proposed mechanism.

In conclusion, we have developed a new Cu-catalyzed thioester–boronic acid desulfitative C–C bond-forming reaction under neutral, aerobic conditions. This reaction expands the scope of sulfur substrates by using attractive, readily available ketene dithioacetals and involves a duel catalysis of Cu for the activation of thioorganics under Pd-free conditions without using S-pendant. By this reaction a series of vinylogous thiolesters and tetrasubstituted olefins were prepared with low cost and easy to handle catalysts.[5] Further studies are in progress.

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